

Single-Beat Determination of Preload Recrutable Stroke Work Relationship: Derivation and Evaluation in Conscious Dogs

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- OBJECTIVES** To derive and evaluate a method of estimating the slope (M_w) of the preload recruitable stroke work (PRSW) relationship between left ventricular stroke work (SW) and end-diastolic volume (EDV) from a single beat.
- BACKGROUND** M_w is a load-insensitive index of contractile function, but its clinical application has been limited by the need to record multiple beats over a wide volume range.
- METHODS** Pressure-volume loops were recorded over a variable preload and afterload range by vena caval and aortic constrictions in 12 conscious dogs instrumented with epicardial dimension transducers and micromanometers. Single-beat M_w (SBM_w) was determined as the ratio $SW/(EDV - V_w)$, where the volume-axis intercept of the PRSW relationship (V_w) (EDV at zero SW) was estimated as $k \cdot EDV_B + (k - 1) \cdot LV_{wall}$, k is the ratio of the epicardial shell volumes corresponding to V_w and baseline EDV (EDV_B) and LV_{wall} is wall volume.
- RESULTS** In the first six dogs, k was found to be essentially constant at 0.7, SBM_w estimates were insensitive to wide preload variation, and the relationship between SBM_w and multibeat M_w determined during caval and aortic constrictions did not differ significantly from the line of identity. When the same constant k value was applied to SBM_w estimation in a different group of six dogs, SBM_w did not differ significantly from multibeat M_w (83 ± 12 erg \cdot cm $^{-3} \cdot 10^3$ and 77 ± 12 erg \cdot cm $^{-3} \cdot 10^3$, respectively), neither changed significantly during aortic constriction and both increased significantly with calcium infusion (107 ± 18 erg \cdot cm $^{-3} \cdot 10^3$ and 95 ± 19 erg \cdot cm $^{-3} \cdot 10^3$, respectively, both $p < 0.05$). Single-beat M_w was less load-dependent, more reproducible and a more sensitive index of inotropic state than two previously described single-beat indexes, single-beat elastance and maximum power divided by EDV^2 .
- CONCLUSIONS** M_w can be determined accurately from a single, steady-state beat in the normal canine heart and is sensitive to inotropic alterations while being insensitive to wide variations in preload and afterload. Single-beat M_w estimation should facilitate noninvasive, load-independent assessment of contractile function. (J Am Coll Cardiol 2000;35:502-13) © 2000 by the American College of Cardiology

The relationship between ventricular stroke work (SW) and end-diastolic volume, termed the preload recruitable stroke work (PRSW) relationship (1), is a highly linear and reproducible index of the contractile state (1-5). The slope of the relationship is sensitive to alterations of the contractile state but insensitive to changes in afterload (1-3).

Clinical application of the PRSW relationship has been limited, however, in part due to the invasive nature of left ventricular (LV) pressure and volume measurements but mainly due to the need to obtain these data over a wide range of end-diastolic volumes. Noninvasive pressure-

volume data can be obtained by combining echocardiographic or radionuclide volume data (6,7) with newer techniques for noninvasive estimation of aortic root pressure (8-11), which is sufficient for the calculation of stroke work (1). Producing a sufficiently wide variation in end-diastolic volume noninvasively, however, remains problematic in clinical studies (4,12-14). Administration of vasoactive agents for this purpose produces only small changes and is subject to confounding direct or reflex inotropic influences, particularly in the absence of autonomic blockade. Even when invasive vena caval occlusion is employed to reduce preload in human subjects, the changes in end-diastolic volume produced are disappointingly modest (4,12-14).

It would be desirable, therefore, if the PRSW relationship could be derived without the necessity of altering preload. The aim of this study was to derive and validate a method

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Abbreviations and Acronyms

ANOVA	= analysis of variance
dP/dt_{\max}	= maximum of the time derivative of ventricular pressure
EDV	= end-diastolic volume
EDV_B	= the baseline, steady-state EDV
$EDV_{B, \text{epi}}$	= the volume within the epicardial shell corresponding to EDV_B
E_{es}	= slope of the ESPVR
ESPVR	= end-systolic pressure-volume relationship
LV	= left ventricle or ventricular
LV_{wall}	= left ventricular wall volume
LVV	= left ventricle chamber volume
M_w	= slope of the PRSW relationship
PRSW	= preload recruitable stroke work
PWR_{\max}/EDV^2	= maximum left ventricular power divided by the square of end-diastolic volume
SBM_w	= single-beat M_w
SD	= standard deviation
SW	= stroke work
V_w	= volume-axis intercept of the PRSW relationship
$V_{w, \text{epi}}$	= the volume within the epicardial shell corresponding to V_w

to determine the PRSW relationship from a single steady-state cardiac beat.

METHODS

The experiments described below were approved by our institutional ethics committee and conformed to the guidelines of the National Health and Medical Research Council of Australia on the care and use of animals.

Experimental preparation. Twelve healthy adult dogs (22 to 42 kg) were anesthetized (halothane 1% to 2% and succinylcholine 0.3 mg/kg intravenously after thiamylal sodium 20 mg/kg intravenously). After left thoracotomy and pericardiotomy, ultrasonic transducers were positioned to measure the epicardial base-apex major axis (a) and anterior-posterior minor axis (b) diameters of the LV (Fig. 1). Pneumatic occluders were positioned around the inferior vena cava and the descending aorta. A heparin-filled silicone catheter was secured in the base of the left atrial appendage. Another catheter with multiple side holes was positioned adjacent to the ventricular epicardium. The pericardium was left open and the thoracotomy repaired. After 7 to 10 days, the transducer leads, catheters and occluder tubing were exteriorized from a subcutaneous pouch. Each animal, lying quietly on its right side, was studied in the conscious state 1 h after light sedation (morphine sulfate, 10 mg intramuscularly).

Data acquisition and experimental protocol. The ultrasonic transducers were coupled to a sonomicrometer.

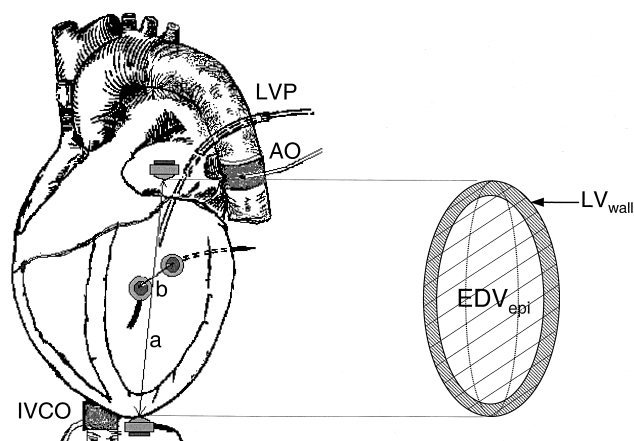


Figure 1. Left panel: Diagram illustrating the placements of the base-apex (dimension a) and anterior-posterior (dimension b) ultrasound dimension transducers, LV micromanometer (LVP) and the pneumatic occluders around the inferior vena cava (IVCO) and descending aorta (AO). Right panel: Schematic diagram of the derived epicardial left ventricular end-diastolic volume (EDV_{epi}), which includes the left ventricular wall volume (LV_{wall}). LV = left ventricle.

Micromanometer-tipped catheters (Millar MPC-500, Houston, Texas) were passed via the implanted silicone catheters to obtain LV and pleural pressures. Pharmacological attenuation of autonomic reflexes was achieved with intravenous administration of propranolol (1 mg/kg) and atropine (0.2 mg/kg).

In the first six dogs instrumented (Group I), data were obtained under steady-state conditions and during transient vena caval occlusion to provide a data set for derivation of a method for single-beat PRSW estimation. The implanted caval occluder was inflated for approximately 10 s. After return of all parameters to their baseline level, the aortic occluder was partially inflated to achieve a stable increase in LV mean ejection pressure of 25%. Transient vena caval occlusion was performed while the aortic constriction was maintained to test the beat-to-beat stability of the single-beat PRSW estimation method over a wider range of pressures and volumes.

The second set of six dogs instrumented (Group II) was used to evaluate the accuracy of the single-beat PRSW method derived in Group I under a variety of hemodynamic and inotropic conditions by comparing the single-beat PRSW estimates with multibeat estimates derived by vena caval occlusion. Data were recorded during transient vena caval occlusions before and during aortic constriction, as described for Group I, and after release of the aortic constriction and restabilization. Transient vena caval occlusion was then performed before and after intravenous infusion of calcium gluconate (15 mg/kg) to increase the inotropic state. Data from the three vena caval occlusions performed before and after aortic constriction and before calcium infusion were employed to determine the reproducibility of single beat and multibeat PRSW estimates.

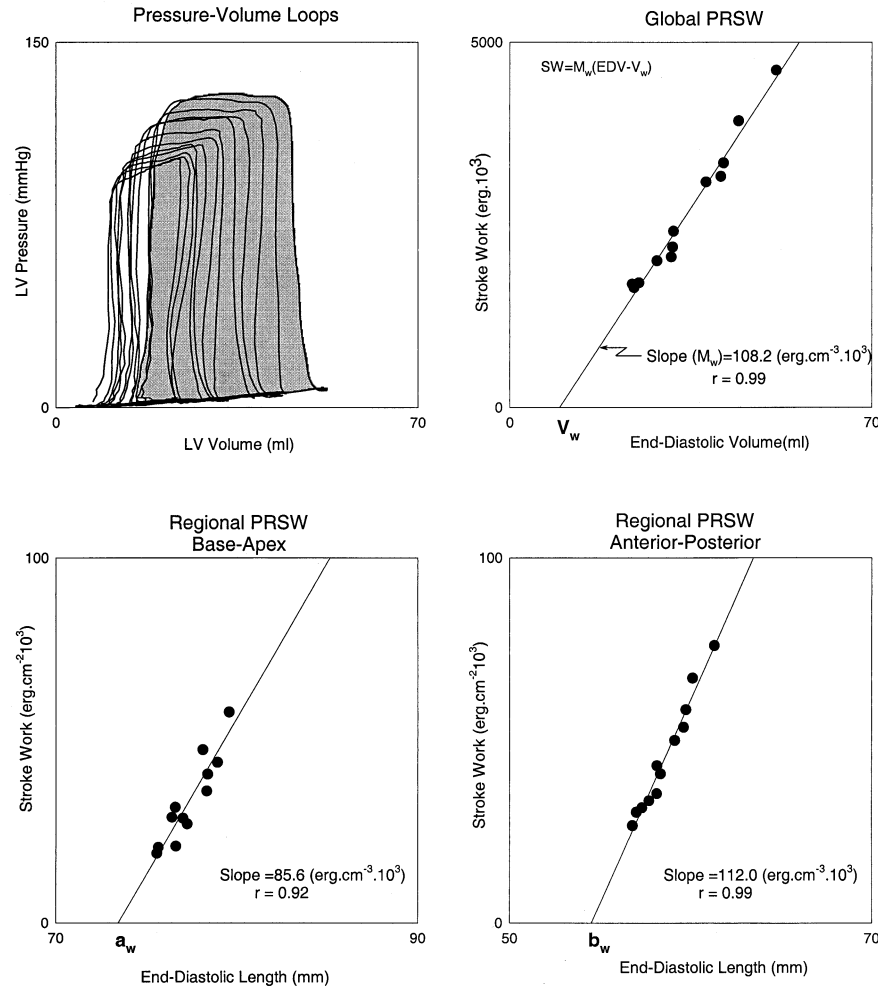


Figure 2. An example of the global and regional PRSW relationships derived from a series of LV pressure-volume loops recorded during a single vena caval occlusion. The global PRSW relationship is the relationship between stroke work, calculated as the pressure-volume loop area (shaded for one beat) and the corresponding end-diastolic volume for the same beat. M_w and V_w are the slope and volume-axis intercept, respectively, of the global PRSW relationship. Regional PRSW relationships are the relationships between regional stroke work (calculated as the pressure-dimension loop area formed by plotting LV pressure against the regional dimension) and the corresponding end-diastolic length of the base-apex or anterior-posterior dimension. a_w and b_w are the corresponding dimension-axis intercepts. LV = left ventricle; M_w = slope of the PRSW relationship; PRSW = preload recruitable stroke work; V_w = volume-axis intercept of the PRSW relationship.

Data analysis. Analog data were digitized in real time at 200 Hz (1). Left ventricular transmural pressure was calculated as chamber pressure minus the adjacent pleural pressure. Left ventricle chamber volume (LVV) was calculated from the ultrasonic epicardial dimension measurements by fitting the major-axis length (a) and the minor-axis diameter (b) to the formula for the volume of a general ellipsoid and subtracting the wall volume (LV_{wall}) determined by water displacement post mortem (Fig. 1) (1).

$$LVV = \frac{\pi}{6} \cdot a \cdot b^2 - LV_{wall} \quad [\text{Equation 1}]$$

Stroke work was calculated as the integral of transmural pressure with respect to chamber volume (i.e., pressure-volume loop area) for each cardiac cycle (Fig. 2). Note that the pressure-volume loop area in Figure 2 should be

distinguished from the “pressure-volume area” index of oxygen consumption defined by Suga as the sum of SW and the area enclosed at end-systole between the end-systolic and end-diastolic pressure-volume relationships, which Suga calls “end-systolic potential energy” (15).

The PRSW relationship was determined by linear regression analysis of the SW and end-diastolic volume (EDV) data obtained during each vena caval occlusion, according to the equation:

$$SW = M_w(EDV - V_w) \quad [\text{Equation 2}]$$

where M_w and V_w are the slope and volume-axis intercept, respectively, of the relationship (Fig. 2) (1).

Single-beat PRSW estimation. Previous studies have demonstrated that V_w remains essentially constant within

an individual, regardless of any short-term loading or inotropic conditions imposed (1-4), so that the slope, M_w , alone reflects changes in the contractile state. Rearranging Equation 2, M_w is given by the equation:

$$M_w = \frac{SW}{(EDV - V_w)} \quad [\text{Equation 3}]$$

It is apparent from Equation 3 that M_w could be calculated from any single beat once the value of V_w was known for the individual subject.

Because V_w is the linearly extrapolated EDV at which no external stroke work is generated, it reflects the aggregate unstressed length of the ventricular muscle fibers in the individual (1,16). We assumed, on the basis of allometric principles (17-19), that individual differences in baseline EDV under similar steady-state hemodynamic conditions reflect individual differences in overall cardiac size and, thus, fiber length, in the same way that ventricular mass (and, thus, wall volume) reflects cardiac size and body size under physiological conditions. From these considerations, we formulated the allometric hypothesis that the ratio of the volume within the epicardial shell corresponding to V_w ($V_{w, \text{epi}}$) to the volume within the epicardial shell corresponding to the baseline, steady-state EDV ($EDV_{B, \text{epi}}$) might be relatively constant, so that:

$$\frac{V_{w, \text{epi}}}{EDV_{B, \text{epi}}} = k \quad [\text{Equation 4}]$$

Expressing this ratio in terms of chamber volumes yields:

$$\frac{V_w + LV_{\text{wall}}}{EDV_B + LV_{\text{wall}}} = k \quad [\text{Equation 5}]$$

Rearranging,

$$V_w = k \cdot EDV_B + (k - 1)LV_{\text{wall}} \quad [\text{Equation 6}]$$

Substituting for V_w in Equation 3 yields the following equation for the single-beat PRSW slope estimate (SBM_w):

$$SBM_w = \frac{SW}{(EDV - k \cdot EDV_B + (1 - k)LV_{\text{wall}})} \quad [\text{Equation 7}]$$

The empirical $V_{w, \text{epi}}/EDV_{B, \text{epi}}$ ratio was determined (Equation 5) from data obtained during the first vena caval occlusion run in the six Group I dogs. V_w was determined by linear regression analysis (Fig. 2). EDV_B was the first recorded baseline EDV value prior to the caval occlusion. To further evaluate the practical utility of the single beat method, SBM_w was calculated with SW estimated as the product of stroke volume and mean ejection pressure rather than pressure-volume loop area (1). We also tested the simpler but related hypothesis that the endocardial volume ratio, V_w/EDV_B , was constant.

From Equation 1, it is apparent that the ratio $V_{w, \text{epi}}/EDV_{B, \text{epi}}$ can also be calculated from empirical data, as follows:

$$\frac{V_{w, \text{epi}}}{EDV_{B, \text{epi}}} = \frac{\frac{\pi}{6} a_w b_w^2}{\frac{\pi}{6} a_{ED} b_{ED}^2} = \left(\frac{a_w}{a_{ED}} \right) \left(\frac{b_w}{b_{ED}} \right)^2 \quad [\text{Equation 8}]$$

where the major and minor dimension ratios, a_w/a_{ED} and b_w/b_{ED} , are directly related to wall fiber length ratios (1). We tested empirically whether the dimensional ratios a_w/a_{ED} and b_w/b_{ED} also were constant in the six Group I dogs. a_w and b_w were determined by performing separate linear regression analyses of the unidimensional SW (pressure-dimension loop area) and end-diastolic lengths in the base-apex (a) and anteroposterior (b) axes (see Fig. 2) (1,16).

Validation of single-beat PRSW estimate. As will be demonstrated, the empirical $V_{w, \text{epi}}/EDV_{B, \text{epi}}$ ratio was found to be essentially constant in the six Group I dogs. The average empirical ratio was then substituted for k in Equation 7 to provide the single-beat estimates of M_w that were compared with multibeat estimates obtained by linear regression analyses of vena caval occlusion data obtained under varying conditions of afterload and contractile state in the Group II dogs. That is, the validity of the assumption of a constant ratio, k , for single-beat estimation of M_w was tested in a different group of dogs from the one in which it was determined initially.

Comparison with other single-beat contractility indexes.

Two previously described single-beat estimates of contractility were determined from the same data set for comparison with single-beat M_w . Single-beat elastance (E_{es}) was determined by the method of Igarashi et al. (20,21) and compared with the multibeat end-systolic pressure-volume relationship (ESPVR) (3). Maximum LV power divided by the square of EDV (PWR_{max}/EDV^2) was determined as described by Kass and Beyar (22).

Statistical analysis. All data are expressed as the mean \pm one standard deviation (SD). Comparisons of steady-state hemodynamic parameters were performed by analysis of variance (ANOVA). The dependence of the various single-beat indexes on preload or afterload was determined by ANOVA for repeated measures. The responses of the multibeat PRSW relationship and ESPVR to altered afterload or inotropic state in Group II dogs were determined by multiple linear regression analyses (23). The relationships between various methods of estimating M_w were compared with the line of identity by a test for coincidence (24). Paired comparisons of single-beat and multibeat estimates were made with the paired t test. A 2×2 ANOVA for repeated measures was used to determine whether there were any significant differences between the responses of the various single-beat estimates to aortic constriction or calcium infusion. The variability of single-beat and multibeat estimates on repeated vena caval occlusions was calculated as SD/mean and expressed as a percentage. Statistical analyses

Table 1. Cardiac Dimensional Ratios and Volume Ratios in Group I Dogs

Dog	Weight (kg)	a_w/a_{ED}	b_w/b_{ED}	$V_{w,epi}/EDV_{B,epi}$ computed with Equation 8	$V_{w,epi}/EDV_{B,epi}$ computed with Equation 5	V_w/EDV_B
1	22	0.89	0.87	0.67	0.70	0.34
2	28	0.93	0.89	0.74	0.73	0.19
3	31	0.95	0.88	0.72	0.71	0.23
4	26	0.93	0.89	0.73	0.74	0.31
5	22	0.93	0.88	0.72	0.72	0.17
6	42	0.96	0.87	0.73	0.73	0.27
Mean \pm SD	29 \pm 7	0.93 \pm 0.04	0.88 \pm 0.01	0.72 \pm 0.02	0.72 \pm 0.01	0.25 \pm 0.13

a_{ED} = baseline, steady-state end-diastolic base-apex dimension; a_w = dimension-axis intercept of the regional PRSW relationship for the base-apex dimension (see Fig. 2); b_{ED} = baseline, steady-state end-diastolic anterior-posterior dimension; b_w = dimension-axis for the anterior-posterior dimension (see Fig. 2); EDV_B = the baseline, steady-state end-diastolic volume; $EDV_{B,epi}$ = the volume of the epicardial shell corresponding to EDV_B ; V_w = volume-axis intercept of the PRSW relationship; $V_{w,epi}$ = the volume of the epicardial shell corresponding to V_w .

were performed with SPSS for Windows, version 8.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Group I. Representative LV pressure-volume loops obtained during a single vena caval occlusion in one dog from Group I are shown in Figure 2 (left upper panel), together with the global PRSW relationship derived from these loops (right upper panel). Also shown in Figure 2 (lower panels) are the corresponding regional PRSW relationships for the base-apex and anteroposterior axes derived from the same data set, demonstrating the empirical determination of V_w , a_w and b_w by linear regression analyses. The global and regional PRSW relationships were linear in all dogs ($r = 0.98 \pm 0.01$ for global, $r = 0.97 \pm 0.03$ for minor axis, $r = 0.88 \pm 0.12$ for major axis). The extent of linear extrapolation beyond the measured data required to determine V_w , a_w and b_w was small.

Table 1 shows the empirical dimension ratios, a_w/a_{ED} and b_w/b_{ED} , obtained in all six Group I dogs. The uniformity of these dimension ratios across the six dogs is quite striking. Also shown in Table 1 are the $V_{w,epi}/EDV_{B,epi}$ ratios computed from these dimension ratios (Equation 8) and the $V_{w,epi}/EDV_{B,epi}$ ratios obtained in the same six dogs based on the measured, individual $V_{w,epi}$ and $EDV_{B,epi}$ values (Equation 5). There is excellent agreement between the two methods of determining the ratios, and these results confirm that the $V_{w,epi}/EDV_{B,epi}$ ratio (k in Equation 7) is remarkably uniform across all dogs at approximately 0.7, despite wide variation in dog weights, from 22 to 42 kg. The corresponding endocardial ratios, V_w/EDV_B , are shown in the last column of Table 1. In contrast to the uniformity of the epicardial ratios, the endocardial ratios are highly variable.

Single beat M_w values were then estimated for all dogs assuming a constant ratio of 0.7 as the value of k in Equation 7 and with SW calculated as the product of stroke volume and mean ejection pressure. Figure 3 shows the relationship between single-beat M_w values for all six Group

I dogs and multibeat estimates derived by linear regression analysis for the vena caval occlusion runs performed before and during aortic constriction, which increased mean ejection pressure from 115 ± 18 to 143 ± 19 mm Hg. The top panel of Figure 3 demonstrates excellent agreement between SW calculated as the product of stroke volume and mean ejection pressure and SW calculated as pressure-volume loop area. As shown in the middle panel, the relationship between calculated single-beat M_w and multibeat M_w was not significantly different from the line of identity (24). Also shown in the middle panel is the relationship between single beat M_w values calculated for the same beats using the individual, measured $V_{w,epi}/EDV_{B,epi}$ ratios from Table 1 for k in Equation 7 and multibeat M_w values; this relationship was not significantly different from that obtained when a constant k value of 0.7 was assumed. The bottom panel of Figure 3 shows a Bland-Altman analysis (25) of the same calculated single-beat M_w ($k = 0.7$) and multibeat M_w data, demonstrating the level of agreement.

To test the load-sensitivity of the single-beat M_w estimation method over a wide range of volumes and pressures, the method was applied to every beat obtained during the vena caval occlusion runs performed in all of the six Group I dogs before and during constriction of the aorta. The results, displayed in Figure 4 (upper panel), confirm that single-beat M_w calculation assuming a constant k value of 0.7 shows no significant dependence on EDV when EDV is reduced to 55% of the baseline value. Since this range of EDV values greatly exceeds the spontaneous variability of steady-state EDV values, single-beat M_w can be considered preload-independent for steady-state data. The data in Figure 4 also indicate that single-beat M_w estimates are insensitive to the increased afterload induced by aortic constriction. In contrast, Figure 4 demonstrates significant preload-dependence of PWR_{max}/EDV^2 (middle panel, $p < 0.05$) and much greater beat-to-beat and within-beat variability (SD/mean) of single-beat E_{es} (lower panel) determined from the same data set. Both of these indexes appeared to exhibit limited afterload sensitivity when com-

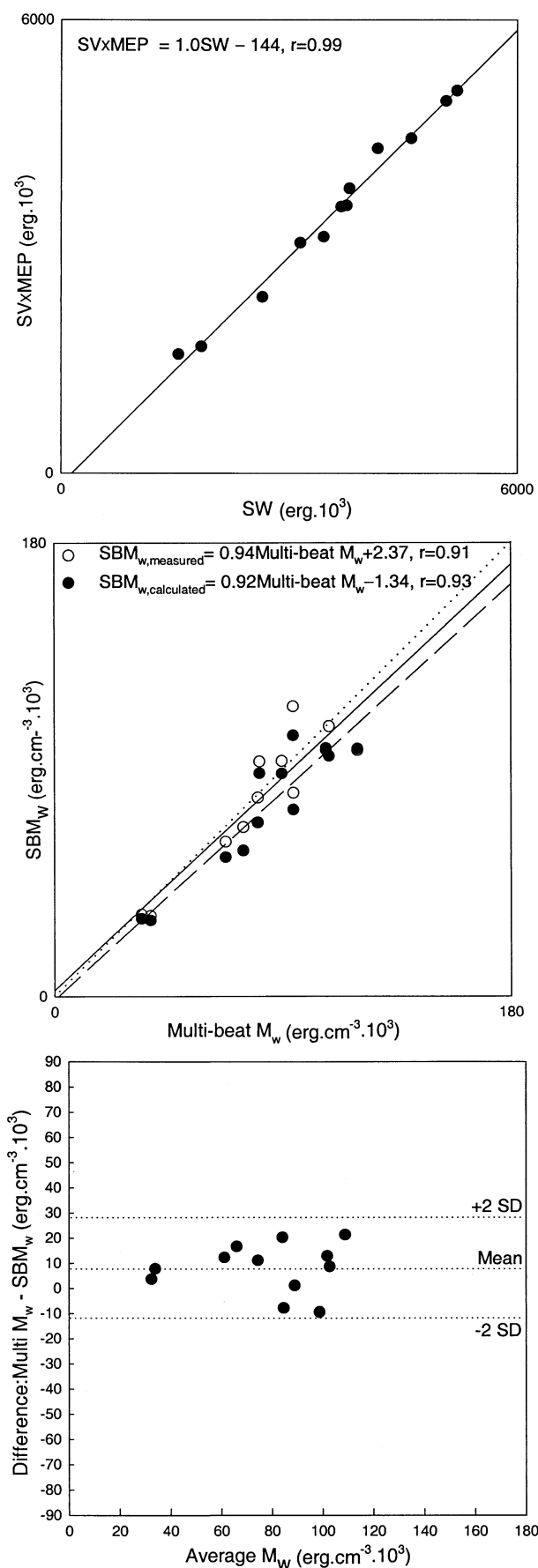


Figure 3. Top panel: Relationship between stroke work calculated as the product of stroke volume and mean ejection pressure and stroke work calculated as pressure-volume loop area based on the same beats from Group I dogs displayed in the middle panel. **Middle panel:** Relationship between single beat M_w (SBM_w) estimates and multibeat M_w measurements in Group I. Multibeat data were obtained during vena caval occlusions performed before and during aortic constriction. Single beat estimates were made from the first steady-state beat preceding each vena caval occlusion. The relationships were not significantly different from the line of identity, whether based on individual measured k values ($SBM_{w, \text{measured}}$, open circles) or calculated assuming k to be constant at 0.7 ($SBM_{w, \text{calculated}}$, closed circles). **Bottom panel:** Bland-Altman analysis (25) of the same calculated SBM_w and multibeat M_w values: the difference between multibeat M_w and SBM_w values is plotted against their average. M_w = slope of the PRSW relationship.

parisons were made at matched EDVs (but see Group II results below).

Group II. The effects of aortic constriction on steady-state hemodynamic parameters in the Group II dogs are summarized in Table 2. The effects of aortic constriction on the multibeat PRSW relationship and single-beat M_w values calculated with a constant k value of 0.7, or based on individual measurements of the ratio in each dog, are summarized in Figure 5. The multibeat PRSW relationships derived from vena caval occlusions performed before and during aortic constriction were highly linear ($r = 0.98 \pm 0.03$ and 0.94 ± 0.10 , respectively). Neither multibeat M_w nor V_w changed significantly with aortic constriction, consistent with previous evidence of the afterload-insensitivity of the relationship (1-3,13). The single-beat M_w estimates did not differ significantly from multibeat values and did not change significantly in response to aortic constriction, regardless of whether k was assumed constant or individual measurements were used.

The effects of calcium infusion on steady-state hemodynamic parameters in Group II are summarized in Table 3. The effects of calcium infusion on the multibeat PRSW relationship and single-beat M_w values are summarized in Figure 6. The multibeat PRSW relationships were highly linear before and after calcium infusion ($r = 0.98 \pm 0.02$ and 0.98 ± 0.03 , respectively). Multibeat M_w increased significantly after calcium infusion ($p < 0.05$) without significant change in V_w , as expected (1-3). The single-beat M_w estimates did not differ significantly from control multibeat M_w values and increased significantly with calcium infusion ($p < 0.05$). There were no statistically significant differences between the multibeat M_w or single-beat M_w responses to calcium, nor were there significant differences between the different methods of calculating single-beat M_w .

The bottom panels of Figures 5 and 6 show the corresponding responses of the ESPVR, single-beat E_{es} and PWR_{max}/EDV^2 to aortic constriction and calcium, respec-

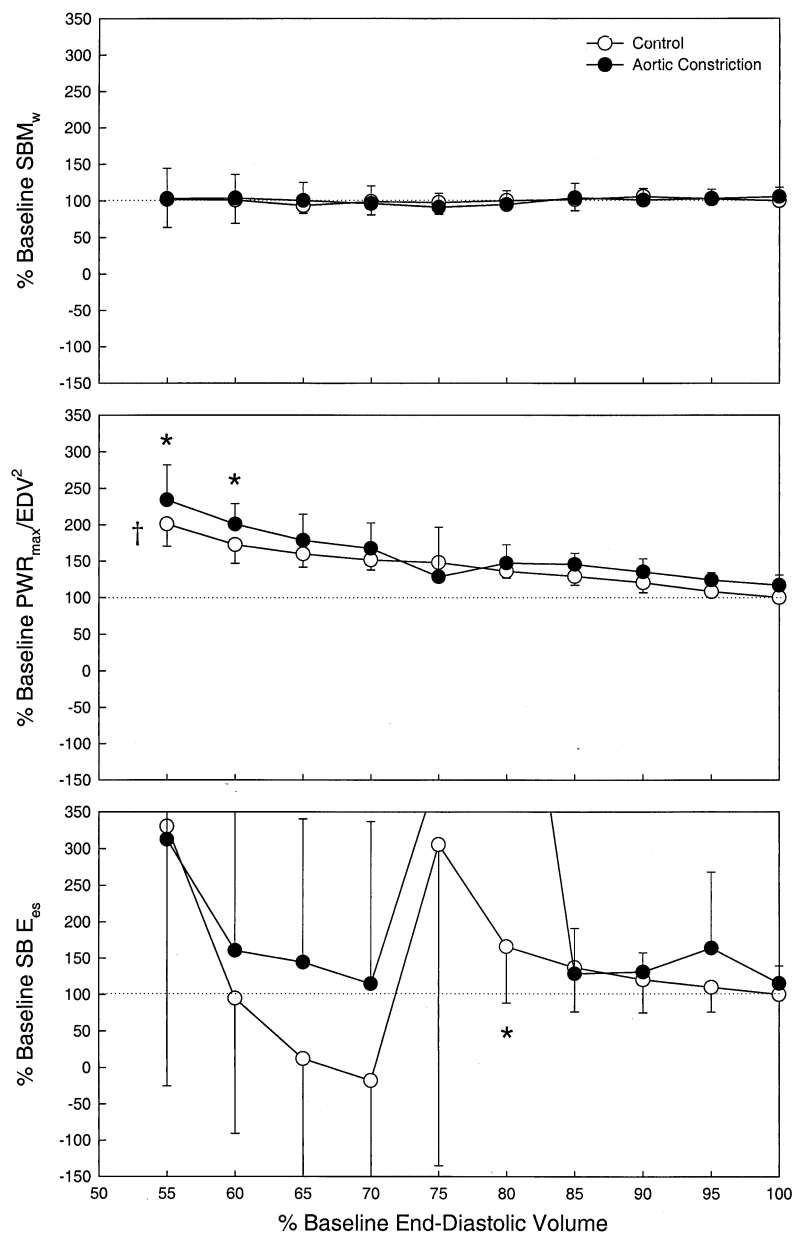


Figure 4. Relationship between beat-to-beat single-beat M_w (SBM_w) (**top panel**) maximum power divided by the square of the end-diastolic volume (PWR_{max}/EDV^2) (**middle panel**) or single-beat elastance ($SB E_{es}$) (**bottom panel**) and end-diastolic volume during the same vena caval occlusion runs performed before (control) and during aortic constriction. End-diastolic volumes are normalized to the value of the first steady-state beat recorded. Values of the three single-beat indexes are normalized to the control steady-state value. Single-beat M_w estimates are insensitive to both preload and afterload. PWR_{max}/EDV^2 is significantly preload sensitive ($\dagger p < 0.05$) but is significantly afterload sensitive only for EDVs less than 65% of baseline ($*p < 0.05$). Single-beat E_{es} is highly variable from beat to beat.

tively. The ESPVR shifted leftward significantly (V_o decreased) with aortic constriction, indicating increased elastance, but single-beat E_{es} and PWR_{max}/EDV^2 both decreased significantly (all $p < 0.05$), indicating afterload sensitivity of both indexes. Note that the afterload sensitivity of these indexes was less apparent in Figure 4 (Group I data) because the comparisons were made at matched EDVs. In contrast, neither single-beat E_{es} nor $PWR_{max}/$

EDV^2 changed significantly with calcium infusion, indicating a lack of inotropic sensitivity, but the ESPVR shifted leftward significantly.

The variability of single-beat M_w estimates on repeated testing with a constant k value of 0.7 ($9.8 \pm 7.0\%$) was not greater than that when individual k values were used ($10.8 \pm 7.1\%$) but somewhat exceeded that of multibeat M_w estimates ($7.2 \pm 4.2\%$). Somewhat greater variability was

Table 2. Effect of Aortic Constriction on Steady-State Hemodynamic Parameters

	HR (beats/min)	LVMEP (mm Hg)	LVEDV (ml)	LVSV (ml)	LVSF (erg·10 ⁻⁴)
Control	134 ± 9	115 ± 13	66 ± 6	27 ± 4	403 ± 66
Aortic constriction	132 ± 7	141 ± 11*	77 ± 8*	24 ± 6	447 ± 140

*p < 0.05 vs. control, t test.

Values are mean ± SD. HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVMEP = left-ventricular mean ejection pressure; LVSF = left ventricular stroke volume; LVSF = left ventricular stroke work.

found for PWR_{max}/EDV^2 ($11.5 \pm 8.0\%$), while single-beat E_{es} was highly variable ($23.4 \pm 19.7\%$).

Single-beat M_w estimation accurately replicated the results of multibeat analyses in Group II despite greater variability of the actual $V_{w,epi}/EDV_{B,epi}$ ratios in Group II (0.67 ± 0.05 ; range 0.62 to 0.73). Shown in Figure 7 are the measured $V_{w,epi}/EDV_{B,epi}$ ratios in all 12 dogs in Group I and Group II, confirming the absence of any relationship with body weight. The wider variability of the ratio in Group II accounts for the wider dispersion of calculated single-beat M_w values (k assumed to be 0.7) about the line of identity with multibeat M_w in Figure 8 (top panel) when compared with single-beat M_w derived from the measured $V_{w,epi}/EDV_{B,epi}$ ratios, but neither relationship differed significantly from the line of identity (24).

For comparison, the relationships between single beat E_{es} or PWR_{max}/EDV^2 and multibeat E_{es} in Group II are shown in the bottom panel of Figure 8; both of these alternative single-beat indexes correlated very poorly with multibeat E_{es} .

DISCUSSION

The most commonly employed clinical indexes of ventricular contractility, the ejection fraction and the maximum of the time derivative of ventricular pressure (dP/dt_{max}), are limited by their strong dependence on cardiac loading conditions. Their continued popularity in clinical practice is a testament both to their ease of measurement and the comparative difficulty of measurement of less load sensitive indexes of contractility (1,2,4,13).

The PRSW relationship. The PRSW relationship, a linear expression of Starling's law of the heart, is load-insensitive (1-5,26,27) and is more strictly linear and more reproducible than other contractility indexes derived from a range of pressure-volume loops, including the ESPVR and the relationship between dP/dt_{max} and EDV (2-5,28-31). Stroke work diminishes at a much faster rate with preload reduction than either end-systolic pressure or dP/dt_{max} , resulting in a wider range of data for linear regression analysis and less extrapolation from the measured data to determine the volume-axis intercept of the PRSW relationship (Fig. 2) (1,2,4). This is particularly advantageous in clinical studies, where the range of data obtainable is much narrower than that achievable in animal experiments (4,5,12-14).

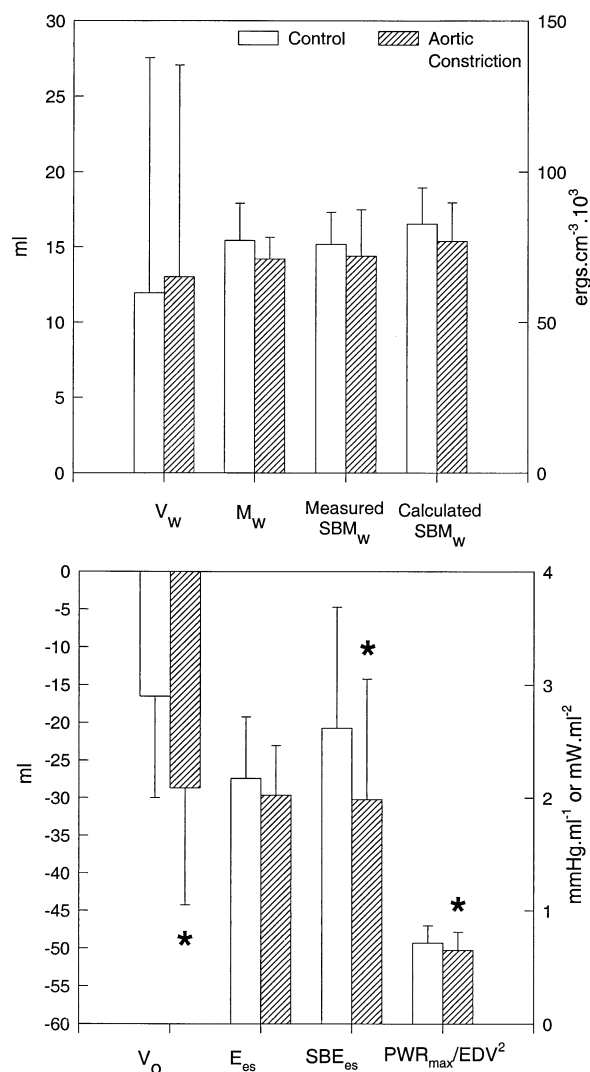


Figure 5. Top panel: The effects of aortic constriction on the mean multibeat PRSW measurements (V_w and M_w) and single-beat M_w (SBM_w) estimates in Group II dogs. Neither multibeat nor single-beat estimates are sensitive to the increased afterload. There were no significant differences between multibeat and single beat M_w values, whether based on individual k values (measured) or a constant k value of 0.7 (calculated). Bottom panel: The corresponding volume-axis intercept (V_o) and slope (E_{es}) of the ESPVR, single-beat E_{es} (SBE_{es}) and PWR_{max}/EDV^2 data (see text). ESPVR = end-systolic pressure-volume relationship; M_w = slope of the PRSW relationship; PRSW = preload recruitable stroke work; PWR_{max}/EDV^2 = maximum left ventricular power divided by the square of end-diastolic volume. V_w = volume-axis intercept of the PRSW relationship. *p < 0.05 vs. control.

Table 3. Effect of Calcium Infusion on Steady-State Hemodynamic Parameters

	HR (beats/min)	LVMEP (mm Hg)	LVEDV (ml)	LVSV (ml)	LVSW (erg·10 ⁴)
Control	112 ± 16	110 ± 14	70 ± 14	29 ± 6	434 ± 91
Calcium	112 ± 17	136 ± 17*	77 ± 10*	35 ± 8*	620 ± 120*

*p < 0.05 vs. control, *t* test.

Values are mean ± SD. HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVMEP = left-ventricular mean ejection pressure; LVSV = left ventricular stroke volume; LVSW = left ventricular stroke work.

The volume-axis intercept of the PRSW relationship, V_w , does not change significantly with altered loading or inotropic conditions, while the slope, M_w , is sensitive to inotropic alterations but insensitive to both preload and afterload (1-4). This study confirmed these characteristics (Fig. 5 and 6). Consequently, once V_w is known in a given individual, M_w can be determined from a single beat (Equation 3), obviating the need to alter loading conditions to determine the relationship.

Limitations of loading alterations. Obviating the need for loading alterations is advantageous not only for reasons of convenience but also because the various options for inducing loading alterations have their own limitations, particularly in clinical studies. Some vasoactive agents may exert direct inotropic effects that confound contractility assessment; the range of pressure-volume alterations achievable with vasoactive agents is usually quite narrow and their administration is not advisable in some clinical situations. Balloon catheter occlusion of the inferior vena cava is invasive and produces much more modest preload reduction in human subjects than in experimental animals (4,12-14). Abdominal compression is generally even less effective in reducing preload, and this technique also increases intrathoracic pressure, altering the relationship between measured ventricular chamber pressure and transmural pressure to an extent that is not quantifiable noninvasively. Finally, no matter which approach is taken to altering loading conditions, acute loading alterations induce reflex autonomic fluctuations that may alter the inotropic state. Autonomic blockade is generally employed to attenuate these influences in animal experiments (1-3), but this is not a practical or desirable approach in most studies of human subjects. Reflex autonomic influences can be minimized by limiting pressure-volume analysis to within 10 seconds of the loading alteration (32), but this approach would further reduce the range of data available for analysis in clinical studies.

Feasibility of noninvasive single beat estimation of contractile state. For all of the reasons noted above, there have been many attempts to define or modify contractility indexes so that they can be derived from steady-state data or from a single beat (20-22,33-35). These efforts have been given greater impetus by the recent development of methods to estimate the aortic root pressure from completely noninvasive peripheral arterial pressure measurements (8-11). When combined with noninvasive methods to determine

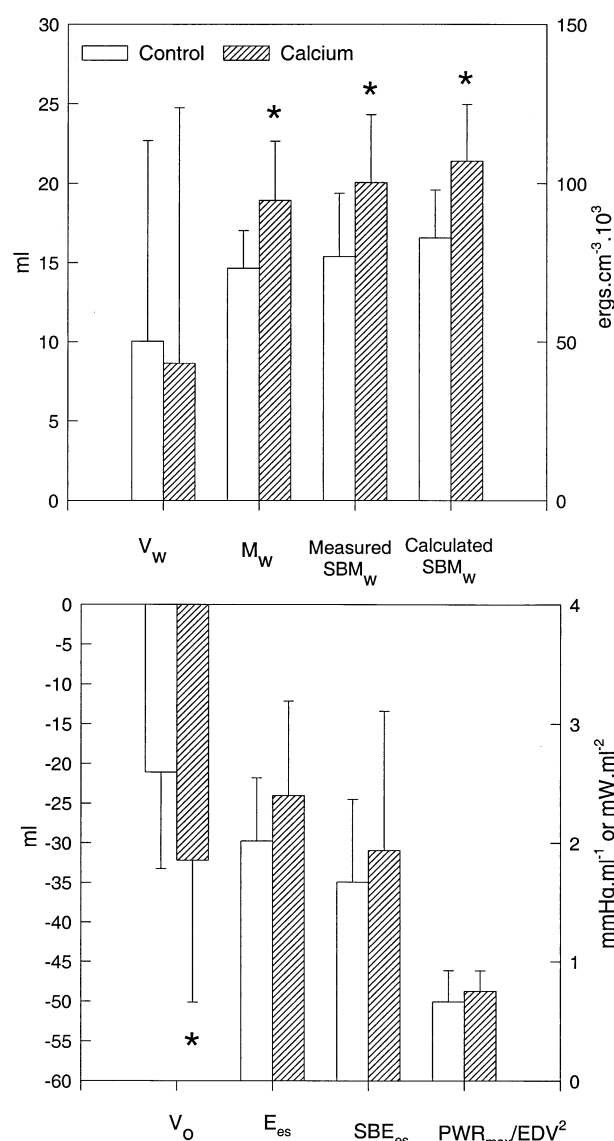


Figure 6. Top panel: The effects of calcium infusion on the mean multibeat and single-beat PRSW estimates in Group II dogs. Both multibeat and single-beat M_w are sensitive to the inotropic stimulation. There were no significant differences between multibeat and single-beat M_w values. Bottom panel: The corresponding ESPVR (V_o and E_{es}), single-beat E_{es} and PWR_{max}/EDV^2 data (see text). E_{es} = slope of the ESPVR; M_w = slope of the PRSW relationship; PWR_{max}/EDV^2 = maximum left ventricular power divided by the square of end-diastolic volume; V_o = volume-axis intercept of the ESPVR; V_w = volume-axis intercept of the PRSW relationship. *p < 0.05 vs. control.

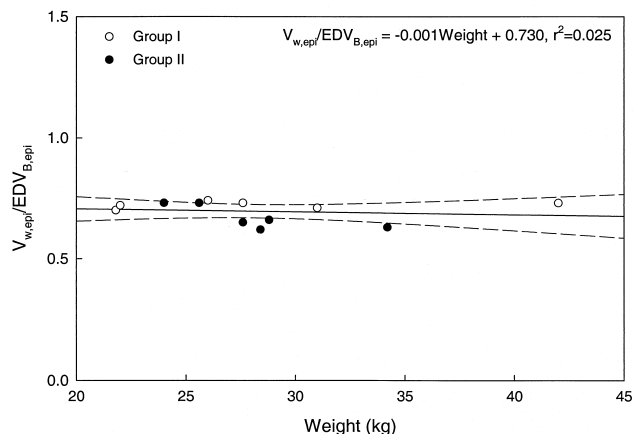


Figure 7. The measured $V_{w,epi}/EDV_{B,epi}$ ratios in all 12 dogs in Groups I and II plotted against the individual body weights of the dogs. The regression line and 95% confidence intervals of the regression are shown: no relationship is evident. $V_{w,epi}$ = the volume within the epicardial shell corresponding to the volume axis intercept of the PRSW relationship; $EDV_{B,epi}$ = the volume within the epicardial shell corresponding to the baseline, steady-state end-diastolic volume.

LV volume such as echocardiography (6,7), these methods make completely noninvasive measurement of LV contractility feasible. Stroke work calculated as the product of stroke volume and mean ejection pressure does not differ appreciably from SW calculated as pressure-volume loop area (1), as confirmed by this study (Fig. 3), and aortic root pressure is almost identical to LV pressure during the ejection period (in the absence of aortic stenosis) (36). Consequently, the pressure-volume data necessary for PRSW estimation can now be obtained noninvasively, and a single beat method for PRSW estimation would greatly increase the feasibility of this noninvasive approach.

Single-beat PRSW estimation. The approach taken to single-beat PRSW estimation in this investigation was based on our hypothesis that the cardiac dimensions at which no external work was predicted by the PRSW relationship would be a relatively constant fraction of the cardiac dimensions under normal, resting hemodynamic conditions. Nevertheless, the uniformity of the axial dimensional fractions actually measured in different dogs (Table 1) was remarkable and permitted calculation of a single epicardial volume ratio of 0.7 that closely approximated the individual volume ratios measured in the different dogs. Application of this constant volume ratio permitted single beat estimates of the PRSW slope that were load-independent over a wide range and that closely approximated multibeat estimates derived by vena caval occlusion, not only in the same group of dogs from which the volume ratio was derived but also in a completely different group of dogs and under conditions of altered afterload and inotropic state that caused significant deviation from the baseline hemodynamics. Moreover, single-beat M_w proved to be load-insensitive and a more

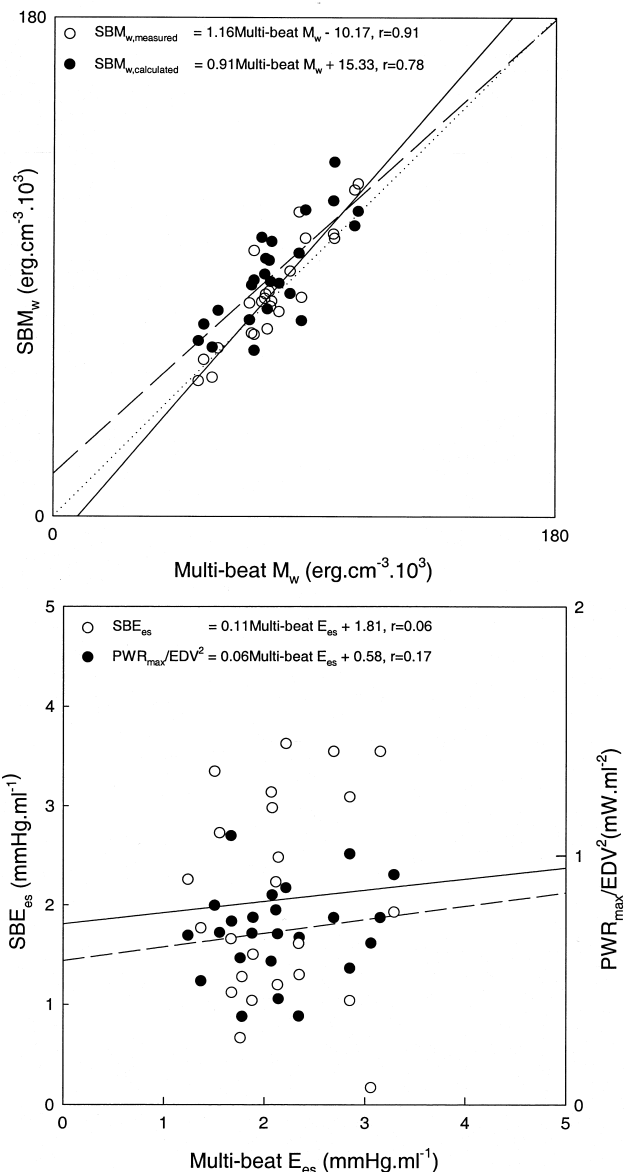


Figure 8. Top panel: Relationship between single-beat M_w (SBM_w) estimates and multibeat M_w measurements in Group II. Multibeat data were obtained during vena caval occlusions performed before and during aortic constriction and calcium infusion. The relationships were not significantly different from the line of identity, whether based on individual measured k values ($SBM_{w,measured}$) or calculated assuming k to be constant at 0.7 ($SBM_{w,calculated}$). **Bottom panel:** Corresponding relationships between single-beat elastance (SBE_{es}) or PWR_{max}/EDV^2 and multibeat elastance (E_{es}). Both single-beat indexes correlated very poorly with multibeat E_{es} . M_w = slope of the PRSW relationship; PWR_{max}/EDV^2 = maximum left ventricular power divided by the square of end-diastolic volume.

reproducible and a more sensitive index of inotropic state than two previously described single-beat indexes, single-beat E_{es} and PWR_{max}/EDV^2 . The latter two indexes were more load-sensitive, and both failed to detect the change in inotropic state with calcium infusion.

Study limitations. The epicardial volume ratio of 0.7 derived in normal dogs may not be precisely applicable to the human heart, but this is of no consequence provided that the human volume ratio is relatively uniform in different individuals. This would seem highly probable given other evidence that the similarity principle is applicable to cardiac geometry across all mammalian species (17-19) but needs to be confirmed. A more important potential limitation of the single beat PRSW estimation method is that the assumption of a constant epicardial volume ratio, which appears to be valid in the normal heart, may not remain valid in pathological states associated with remodelling of ventricular geometry. On the other hand, it is well documented that the increase in ventricular dimensions consequent to chronic volume overload or ischemia is also associated with an increase in the volume-axis intercept of the global PRSW relationship, or the length-axis intercept of the regional PRSW relationship (16,37).

In fact, in a previous study of LV adaptation to the creation of aortic regurgitation in conscious dogs (37), the mean $V_{w,epi}/EDV_{B,epi}$ ratio (calculated from data in Table 1 of reference 37) did not change significantly from the control value of 0.66 either early (1-3 weeks) or late (4-9 weeks) after the onset of regurgitation despite the fact that chamber volume increased most in the early period, while the mean increase of 13% in wall volume occurred mostly in the later period. It must be acknowledged, however, that the ventricular remodelling responses to pressure overload or dilated cardiomyopathy differ from those to chronic volume overload, and the epicardial volume ratio might well be different in these situations. The assumption of a constant k value may be particularly problematic in the presence of ischemic heart disease with regional LV dysfunction. Further studies will be required to examine the responses of the epicardial volume ratio to these remodelling situations.

These potential limitations of an assumed constant value of k are not relevant, however, to most situations in which contractility is assessed in either animal experiments or clinical studies. In most situations, the question addressed is whether contractility has changed with a given intervention relative to a control measurement in the same individual. Provided that the nature and the time-frame of the intervention are not such that ventricular remodelling would be expected, the results of this investigation suggest that single-beat PRSW estimation would provide the same information as the multibeat method.

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